

**REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)****RECEIVED****MAR 3 1 2003**

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☐ (A) referred to in:United States Patent Application Publication No. 6,177,401, page \_\_\_\_\_, line \_\_\_\_\_,

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US006177401B1

(12) **United States Patent**  
Ullrich et al.

(10) Patent No.: **US 6,177,401 B1**  
(45) Date of Patent: **Jan. 23, 2001**

(54) **USE OF ORGANIC COMPOUNDS FOR THE INHIBITION OF FLK-1 MEDIATED VASCULOGENESIS AND ANGIOGENESIS**

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(\*) Notice: Under 35 U.S.C. 154(b), the term of this patent shall be extended for 0 days.

(21) Appl. No.: 08/193,829

(22) Filed: Feb. 9, 1994

**Related U.S. Application Data**

(63) Continuation-in-part of application No. 08/038,596, filed on Mar. 26, 1993, now abandoned, which is a continuation-in-part of application No. 07/975,750, filed on Nov. 13, 1992, now abandoned.

(51) Int. Cl.<sup>7</sup> ..... A61K 31/00

(52) U.S. Cl. .... 514/1; 435/7.2; 436/501; 530/350; 530/399

(58) Field of Search ..... 536/23.5; 435/69.1, 435/172.1, 240.2, 252.3, 320.1, 325, 361, 7.2; 424/93.2; 514/44, 1; 935/32, 57, 70, 71; 436/501; 530/399, 350

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(57) **ABSTRACT**

The present invention relates to the use of proteins, peptides and organic molecules capable of modulating Flk-1 receptor signal transduction in order to inhibit or promote angiogenesis and vasculogenesis. The invention is based, in part, on the demonstration that Flk-1 tyrosine kinase receptor expression is associated with endothelial cells and the identification of vascular endothelial growth factor (VEGF) as the high affinity ligand of Flk-1. These results indicate a major role for Flk-1 in the signaling system during vasculogenesis and angiogenesis. Engineering of host cells that express Flk-1 and the uses of expressed Flk-1 to evaluate and screen for drugs and analogs of VEGF involved in Flk-1 modulation by either agonist or antagonist activities is described.

The invention also relates to the use of FLK-1 ligands, including VEGF agonists and antagonists, in the treatment of disorders, including cancer, by modulating vasculogenesis and angiogenesis.

**16 Claims, 25 Drawing Sheets**